introducing first and second sequence specific primers to said circular cDNA, wherein said first and second primers are designed to hybridize to from about 4 to about 35 contiguous bases from a sequence known or suspected to be present in said circular cDNA; and

initiating a primer extension amplification reaction to increase copy number of said circular cDNA.

REMARKS

Applicants note at the outset that the specification has been amended to correct an error committed by Applicants in its response filed October 15, 2001. In that response, Applicants erroneously replaced the paragraph at page 3, line 8 with an unrelated paragraph. This unrelated paragraph was actually an amended version of the paragraph located at page 10, line 10. Applicants also erroneously attached to its response a "marked up" version of the paragraph from page 10, line 10 to show the changes made. This was an error because, in a literal sense, there was no corresponding amendment contained in the response itself. Clearly, Applicants' intent was to amend the paragraph at page 10, line 10 by removing the embedded hyperlink. Applicants respectfully submit that this error was made in good faith and that no new matter was added to the application by virtue of the replacement of the paragraph at page 3, line 8, since the "replacing" paragraph was actually an amended version of a paragraph located at page 10, line 10. Applicants also respectfully submit that the amendments contained herein have corrected the error, and that, once again, no new matter has been added to the application.

Claim Rejections

35 U.S.C. § 112, Second Paragraph

The Examiner rejects claim 20 under 35 U.S.C. § 112, second paragraph, as being incomplete for omitting essential elements. Although not acceding to the rejection, Applicants

note that the amendments contained herein have rendered this rejection moot, and therefore respectfully request its withdrawal.

35 U.S.C. § 102(b)

The Examiner rejects claims 1, 3, 4, 7, 12, 13, 24, and 25 under 35 U.S.C. § 102(b) as being anticipated by United States Patent No. 4,994,370 (Silver *et al.*). Although not acceding to the rejection, Applicants note that the amendments contained herein have rendered this rejection moot, and therefore respectfully request its withdrawal.

35 U.S.C. § 103(a)

The Examiner rejects claims 1-20 and 24-27 under 35 U.S.C. § 103(a) as being obvious over Silver *et al.* in view of "Protocol – Reverse Transcriptase," in MOLECULAR BIOTECHNOLOGY, vol. 8, Humana Press Inc., pp. 61-77 (1997) (Gerard *et al.*). Applicants respectfully disagree.

The PTO bears the burden of establishing a case of prima facie obviousness. *See, e.g., In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988). "To establish a *prima facie* case of obviousness based on a combination of the content of various references, there must be some teaching, suggestion or motivation in the prior art to make the specific combination that was made by the applicant." *In re Dance*, 160 F.3d 1339, 1343, 48 U.S.P.Q.2d 1635, 1637 (Fed. Cir. 1998).

Although the suggestion to combine references may flow from the nature of the problem, "[d]efining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness." *Monarch Knitting Machine Corp. v. Sulzer Morat Gmbh*, 139 F.3d 877, 880 45 U.S.P.Q.2d 1977, 1981 (Fed. Cir. 1998). Federal Circuit case law makes clear that the best defense against hindsight-based obviousness analysis is "the *rigorous* application of the requirement for a showing of a teaching or motivation to combine the prior art references."

Ecolochem v. Southern California Edison Co., 227 F.3d 1361, 1371, 56 U.S.P.Q.2d 1065, 1073 (emphasis added).

As support for its position that claims 1-20 and 24-27 are obvious, the Examiner states:

> [I]t would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made, to modify a method of amplifying single-stranded circular DNA as taught by Silver et al. with the amplification of mRNA with RNase H⁻ reverse transcriptase as taught by Gerard et al. to achieve the expected advantage of obtaining single strand nucleic acid *because Silver et al. states that 'amplification of specific exons, provides a way to rapidly search for mutations in patients in whom it is difficult to obtain mRNA for cDNA cloning.'* One such alternative form of amplification of exons, expressly motivated by Gerard et al. it to obtain amplification of single strand mRNA because Gerard et al [sic] states that 'reverse transcriptase catalyzes cDNA synthesis more efficiently in the absence of RNase H.'

PTO Paper No. 8, at 5-6 (citations omitted) (emphasis added). As the Examiner notes, one of the obstacles sought to be circumvented by Silver *et al.* was the necessity for obtaining mRNA from patients in whom a specific gene defect was suspected prior to screening for mutations. However, Applicants' claims, as amended herein, specifically *require* obtaining mRNA in order to amplify/synthesize cDNA. As such, Applicants respectfully submit that one of ordinary skill in the art would not have been motivated to modify the teachings of Silver *et al.* with those of Gerard *et al.* in order to achieve the amplification of cDNA as claimed.

CONCLUSION

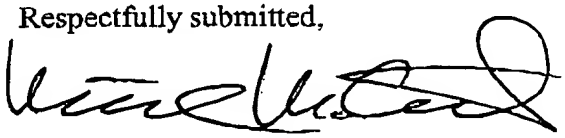
Support for the amendments contained herein may be found in both the specification and claims as originally filed. Applicants respectfully submit that these amendments, as well as Applicants' remarks, place the captioned application in condition for allowance.

No fees or extensions of time are believed to be due in connection with this amendment; however, consider this a request for any extension inadvertently omitted, and charge any additional fees to Deposit Account No. 26-0084.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**AMENDMENT--VERSION WITH MARKINGS TO SHOW CHANGES MADE.**"

Reconsideration and allowance is respectfully requested.

Respectfully submitted,



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Application No. 09/780,762

AMENDMENT — VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification

The paragraph at page 10, beginning at line 10, has been amended as follows:

Once the circular nucleic acid is formed, then a template extension amplification reaction is carried out with gene specific primers. The design of the first and second primers differs from that of traditional PCR of cDNA first in that using a single nucleic acid strand as template. The primers are instead designed so that each one has a 3' end of the primer which is toward either the 5' or 3' end of the polynucleotide. This means that the forward primer will typically be towards the 3' end of the molecule and the reverse primer will be towards the 5' end of the molecule. For example, if a known sequence comprises 5'-ATATATATGCGCGCGC-3' a forward primer would be 5'-CGCGCGCG-3' to hybridize with the 3' end of the molecule and the second or reverse primer would be 5'-ATATATAT-3' to hybridize with the 5' end of the molecule and having its 3' end towards the 5' of the target gene. See Figure 1. Design of primers for amplification and extension reactions are commonly known in the art of PCR amplification and the remainder of primer design is standard. A brief summary of oligonucleotide primer design is disclosed herein. In addition a discussion of primer design can be located in "Molecular biology Techniques Manual" third edition CRC Press, Editors, Coyne et al. [available at www.uct.ac.za/microbiology/pcroptim.htm.] In addition, there are a number of publically and commercially available computer programs to aid in design of primers including, BLAST, PrimerGen, Primer (Stanford), Amplify, Primer Design 1.04, PC-Rare, CODEHOP, Primer 3, and Net Primer (Premier Biosoft Int'l).

In the Claims

Claims 1, 6, 9-12, 15-17, 26 and 27 have been amended as follows:

1. (Amended)

A method for amplifying a cDNA [polynucleotide sequence] comprising:

obtaining an mRNA;

reverse transcribing [contacting] the mRNA into cDNA with reverse transcriptase without RNase H activity so that a [first strand] cDNA-mRNA complex is formed;[, and]
degrading the mRNA from the cDNA-mRNA complex to form a linear cDNA;
[obtaining a linear, single strand polynucleotide sample;]
ligating the ends of said linear cDNA [sample] to form a circular cDNA [shaped sample];
introducing first and second sequence specific primers to said circular cDNA [sample]; and
initiating a primer extension amplification reaction to increase copy number of said circular cDNA [sample].

6. (Amended)

The method of claim 1 [2] further comprising the step of:
harvesting said amplified cDNA [nucleotide product].

9. (Amended)

The method of claim 1 wherein said first and second primers are designed to hybridize to from about 4 to about 35 contiguous bases from a sequence known or suspected to be present in said circular cDNA [nucleic acid sample].

10. (Amended)

The method of claim 1 wherein said first primer comprises a 3' end of the same which is toward the 5' end of the circular cDNA [nucleic acid sample].

11. (Amended)

The method of claim 1 wherein one of said primers comprises a 3'end of the same which is toward the 3' end of said circular cDNA [nucleic acid sample].

12. (Twice Amended)

A method for amplifying a cDNA, [nucleic acid molecule] including the 5' and 3' ends, comprising:
obtaining an mRNA;
contacting the mRNA with reverse transcriptase without RNase H so that a cDNA-mRNA complex is formed;
degrading the mRNA from the cDNA-mRNA complex to form a linear cDNA;
circularizing said linear cDNA [nucleic acid molecule];

contacting the circularized cDNA [said nucleic acid] with first and second sequence specific primers; and

introducing a polymerase and a supply of nucleotide bases to said circularized cDNA [nucleic acid molecule] so that an amplification reaction occurs,[;] wherein said region of said cDNA [nucleic acid molecule] outside of said first and second primers including the 3' and 5' ends of said cDNA [molecule] is amplified.

15. (Amended)

The method of claim 1 wherein said forward and reverse primers are designed to hybridize to from about 4 to about 35 contiguous bases from a sequence known or suspected to be present in said circular cDNA [nucleic acid sample].

16. (Amended)

The method of claim 1 wherein said one of said primers comprises a 3' end of the same which is toward the 5' end of the circular cDNA [nucleic acid sample].

17. (Amended)

The method of claim 1 wherein one of said primers comprises a 3'end of the same which is toward the 3' end of said circular cDNA [nucleic acid sample].

26. (Amended)

A method for amplifying a cDNA [polynucleotide sequence] comprising:

obtaining an mRNA;

reverse transcribing the mRNA into cDNA with reverse transcriptase without RNase H activity so that a cDNA-mRNA complex is formed;

degrading the mRNA from the cDNA-mRNA complex to form a linear cDNA;

[obtaining a linear, single strand polynucleotide sample;]

ligating the ends of said linear cDNA [sample] to form a circular cDNA [shaped sample];

introducing first and second sequence specific primers to said circular cDNA [sample], wherein said primers are degenerate primers; and

initiating a primer extension amplification reaction to increase copy number of said circular cDNA [sample].

27. (Amended)

A method for amplifying a cDNA [polynucleotide sequence] comprising:

obtaining an mRNA;

reverse transcribing the mRNA into cDNA with reverse transcriptase without RNase H activity so that a cDNA-mRNA complex is formed;

degrading the mRNA from the cDNA-mRNA complex to form a linear cDNA;

[obtaining a linear, single strand polynucleotide sample;]

ligating the ends of said circular cDNA [sample] to form a circular cDNA [shaped sample];

introducing first and second sequence specific primers to said circular cDNA [sample], wherein said first and second primers are designed to hybridize to from about 4 to about 35 contiguous bases from a sequence known or suspected to be present in said circular cDNA [nucleic acid sample]; and

initiating a primer extension amplification reaction to increase copy number of said circular cDNA [sample].